

CLAIMS

1. A polynucleotide comprising a polynucleotide selected from the group consisting of:
 - (a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 75, 76, 81, 82, 87, 88, 93, 94, 99, 100, 105, 106, 111, 112, 117, 118, 123, 124, 129, 130, 135, 136, 141, 142, 147, 148, 153, 154, 159, 160, 165, 166, 171, 172, 177, 178, 183, 184, 189, 190, 195, 196, 201, 202, 207, 208, 213, 214, 219, 220, 225, 226, 231, 232, 237, 238, 243, 244, 249, 250, 255, 256, 261, 262, 267, 268, 273, 274, 279, 280, 285, 286, 291, 292, 297, 298, 303, 304, 309, 310, 315, 316, 321, 322, 329, 330, 333, 334, 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397 or 398;
 - (b) a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 324, 326, 328, 401 or 403;
 - (c) a polynucleotide capable of hybridizing to a MRP-1 gene, wherein said polynucleotide is having a substitution or deletion of at least one nucleotide at a position corresponding to position 124667 of the MRP-1 gene (Accession No: AC026452), 1884, 1720 to 1723, 1163, 926, 437, 381, 233, 189, 440 or 1625 of the MRP-1 gene (Accession No: U07050), 39508 of the MRP-1 gene (GI No: 7209451), 79, 88 or 249 of the MRP-1 gene (Accession No: AF022830), 95 or 259 of the MRP-1 gene (Accession No: AF022831), 57998, 57853 or 53282 of the MRP-1 gene (GI No: 7209451), 137710, 137667, 38646 or 137647 of the MRP-1 gene (Accession No: AC026452), 27159, 27258, 34206 to 34207, 34218, 34215, 55156 or 55472 of the MRP-1 gene (Accession No: AC003026), 14008, 17970, 18195, 21133, 18067, 17900 of the MRP-1 gene (Accession No: U91318), or 150727 or 33551 of the MRP-1 gene (Accession No: AC025277), 174 of the MRP-1 gene (Accession No: AF022828), 248 or 258 of the MRP-1 gene (Accession No: AF022829), 51798 or 50892 of the MRP-1 gene (Accession No: GI 3582311), 37971 of the MRP-1 gene (Accession No: GI 7363401), 55296, 55132, 55114,

55112 or 20097 to 20099 of the MRP-1 gene (Accession No: GI 2815549), 109 to 122, 76 to 78, 73 to 78, 70 to 78, 67 to 78 or 58 to 78 of the MRP-1 gene (Accession No: GI 4826837), 60357, 61786 or 39541 of the MRP-1 gene (Accession No: GI 7209451) or a insertion of at least one nucleotide at a position corresponding to position 55156/55157 of the MRP-1 gene (Accession No: AC003026) or 437/438 or 926/927 of the MRP-1 gene (Accession No: U07050) or 76437/76438 of the MRP-1 gene (Accession No: GI 7209451);

- (d) a polynucleotide capable of hybridizing to a MRP-1 gene, wherein said polynucleotide is having at a position corresponding to position 124667 of the MRP-1 gene (Accession No: AC026452) a C, at a position corresponding to position 1884 of the MRP-1 gene (Accession No: U07050) a A, at a position corresponding to position 1720 to 1723 of the MRP-1 gene (Accession No: U07050) a deletion, at a position corresponding to position 1163 of the MRP-1 gene (Accession No: U07050) a T, at a position corresponding to position 926/927 of the MRP-1 gene (Accession No: U07050) a insertion, at a position corresponding to position 437/438 of the MRP-1 gene (Accession No: U07050) a insertion, at a position corresponding to position 381 of the MRP-1 gene (Accession No: U07050) a G, at a position corresponding to position 233 of the MRP-1 gene (Accession No: U07050) an A, at a position corresponding to position 189 of the MRP-1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP-1 gene (GI No: 7209451) an A, at a position corresponding to position 174 of the MRP-1 gene (Accession No: AF022828) a T, at a position corresponding to position 248 of the MRP-1 gene (Accession No: AF022829) an A, at a position corresponding to position 258 of the MRP-1 gene (Accession No: AF022829) a G, at a position corresponding to position 79 of the MRP-1 gene (Accession No: AF022830) an A, at a position corresponding to position 88 of the MRP-1 gene (Accession No: AF022830) a C, at a position corresponding to position 249 of the MRP-1 gene (Accession No: AF022830) a G, at a position corresponding to position 95 of the MRP-1 gene (Accession

No: AF022831) a C, at a position corresponding to position 259 of the MRP-1 gene (Accession No: AF022831) a G, at a position corresponding to position 57998 of the MRP-1 gene (GI No: 7209451) a T, at a position corresponding to position 57853 of the MRP-1 gene (GI No: 7209451) a T, at a position corresponding to position 53282 of the MRP-1 gene (GI No: 7209451) a G, at a position corresponding to position 137710 of the MRP-1 gene (Accession No: AC026452) a G, at a position corresponding to position 137667 of the MRP-1 gene (Accession No: AC026452) a T, at a position corresponding to position 137647 of the MRP-1 gene (Accession No: AC026452) a T, at a position corresponding to position 27159 of the MRP-1 gene (Accession No: AC003026) a C, at a position corresponding to position 27258 of the MRP-1 gene (Accession No: AC003026) an A, at a position corresponding to position 34206 to 34207 of the MRP-1 gene (Accession No: AC003026) a deletion, at a position corresponding to position 34215 of the MRP-1 gene (Accession No: AC003026) a C, at a position corresponding to position 55156/55157 of the MRP-1 gene (Accession No: AC003026) a insertion, at a position corresponding to position 55472 of the MRP-1 gene (Accession No: AC003026) a C, at a position corresponding to position 14008 of the MRP-1 gene (Accession No: U91318) an A, at a position corresponding to position 150727 of the MRP-1 gene (Accession No: AC025277) an A, at a position corresponding to position 17970 of the MRP-1 gene (Accession No: U91318) a deletion, at a position corresponding to position 18195 of the MRP-1 gene (Accession No: U91318) an A, at a position corresponding to position 21133 of the MRP-1 gene (Accession No: U91318) an A, at a position corresponding to position 34218 of the MRP-1 gene (Accession No: AC003026) an A, at a position corresponding to position 18067 of the MRP-1 gene (Accession No: U91318) a T, at a position corresponding to position 440 of the MRP-1 gene (Accession No: U07050) a T, at a position corresponding to position 1625 of the MRP-1 gene (Accession No: U07050) an A, at a position corresponding to position 17900 of the MRP-1 gene (Accession No: U91318) a T, at a

position corresponding to position 38646 of the MRP-1 gene (Accession No: AC026452) a C, at a position corresponding to position 33551 of the MRP-1 gene (Accession No: AC025277) an A, at a position corresponding to position 51798 of the MRP-1 gene (Accession No: 3582311) an G, at a position corresponding to position 37971 of the MRP-1 gene (Accession No: 7363401) an A, at a position corresponding to position 50892 of the MRP-1 gene (Accession No: 3582311) an A, at a position corresponding to position 55296 of the MRP-1 gene (Accession No: 2815549) an A, at a position corresponding to position 55132 of the MRP-1 gene (Accession No: 2815549) an A, at a position corresponding to position 55114 of the MRP-1 gene (Accession No: 2815549) an G, at a position corresponding to position 55112 of the MRP-1 gene (Accession No: 2815549) an G, at a position corresponding to position 109 to 122 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 76 to 78 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 73 to 78 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 70 to 78 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 67 to 78 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 58 to 78 of the MRP-1 gene (Accession No: 4826837) deletions, at a position corresponding to position 20097 to 20099 of the MRP-1 gene (Accession No: 2815549) deletions, at a position corresponding to position 60357 of the MRP-1 gene (Accession No: 7209451) a T, at a position corresponding to position 61786 of the MRP-1 gene (Accession No: 7209451) an A, at a position corresponding to position 76437/76438 of the MRP-1 gene (Accession No: 7209451) an insertion or at a position corresponding to position 39541 of the MRP-1 gene (Accession No: 7209451) an A;

- (e) a polynucleotide encoding an MRP-1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at position 329, 433 or 723 of the MRP-1 polypeptide (Accession No:

P33527) or 73 or 989 of the MRP-1 polypeptide (Accession No: GI 2828206); and

- (f) a polynucleotide encoding an MRP-1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at position 329, Arg to Ser at position 433 or Arg to Gln at position 723 of the MRP-1 polypeptide (Accession No: P33527) or Thr to Ile at position 73 or Ala to Thr at position 989 of the MRP-1 polypeptide (Accession No: GI 2828206).
- 2. A polynucleotide of claim 1, wherein said polynucleotide is associated with a disease selected from the group consisting of cancer diseases and multidrug resistance related diseases.
 - 3. A polynucleotide of any one of claims 1 or 2 which is DNA or RNA.
 - 4. A gene comprising the polynucleotide of any one of claims 1 or 2.
 - 5. The gene of claim 4, wherein a nucleotide deletion, addition and/or substitution results in altered expression of the variant gene compared to the corresponding wild type gene.
 - 6. A vector comprising a polynucleotide of any one of claims 1 to 3 or the gene of claim 4 or 5.
 - 7. The vector of claim 6, wherein the polynucleotide is operatively linked to expression control sequences allowing expression in prokaryotic or eukaryotic cells or isolated fractions thereof.
 - 8. A host cell genetically engineered with the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5 or the vector of claim 6 or 7.
 - 9. A method for producing a molecular variant MRP-1 polypeptide or fragment thereof comprising

- (a) culturing the host cell of claim 8; and
 - (b) recovering said protein or fragment from the culture.
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- 10. A method for producing cells capable of expressing a molecular variant MRP-1 polypeptide comprising genetically engineering cells with the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5 or the vector of claim 6 or 7.
 - 11. A polypeptide or fragment thereof encoded by the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5 or obtainable by the method of claim 9 or from cells produced by the method of claim 10.
 - 12. An antibody which binds specifically to the polypeptide of claim 11.
 - 13. The antibody of claim 12 which specifically recognizes an epitope containing one or more amino acid substitution(s) resulting from a nucleotide exchange as defined in claim 1 or 5.
 - 14. The antibody of claim 12 or 13 which is monoclonal or polyclonal.
 - 15. A transgenic non-human animal comprising at least one polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5 or the vector of claim 6 or 7.
 - 16. The transgenic non-human animal of claim 15 which is a mouse, a rat or a zebrafish.
 - 17. A solid support comprising one or a plurality of the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5, the vector of claim 6 or 7, the polypeptide of claim 11, the antibody of claim 12 or 13 or the host cell of claim 8 in immobilized form.
 - 18. The solid support of claim 17, wherein said solid support is a membrane, a glass-or polypropylene- or silicon-chip, are oligonucleotide-conjugated beads or a bead array, which is assembled on an optical filter substrate.

19. An in vitro method for identifying a single nucleotide polymorphism said method comprising the steps of:
 - (a) isolating a polynucleotide of any one claims 1 to 3 or the gene of claim 4 or 5 from a plurality of subgroups of individuals, wherein one subgroup has no prevalence for a MRP-1 associated disease and at least one or more further subgroup(s) do have prevalence for a MRP-1 associated disease; and
 - (b) identifying a single nucleotide polymorphism by comparing the nucleic acid sequence of said polynucleotide or said gene of said one subgroup having no prevalence for a MRP-1 associated disease with said at least one or more further subgroup(s) having a prevalence for a MRP-1 associated disease.
20. A method for identifying and obtaining a pro-drug or a drug capable of modulating the activity of a molecular variant of a MRP-1 polypeptide comprising the steps of:
 - (a) contacting the polypeptide of claim 11, the solid support of claim 17 or 18, a cell expressing a molecular variant gene comprising a polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5 or the vector of claim 6 or 7 in the presence of components capable of providing a detectable signal in response to drug activity with a compound to be screened for pro-drug or drug activity; and
 - (b) detecting the presence or absence of a signal or increase or decrease of a signal generated from the pro-drug or the drug activity, wherein the absence, presence, increase or decrease of the signal is indicative for a putative pro-drug or drug.
21. A method for identifying and obtaining an inhibitor of the activity of a molecular variant of a MRP-1 polypeptide comprising the steps of:
 - (a) contacting the protein of claim 11, the solid support of claim 17 or 18 or a cell expressing a molecular variant gene comprising a polynucleotide of any one of claims 1 to 3 or the gene of claim 4 or 5 or the vector of

- claim 6 or 7 in the presence of components capable of providing a detectable signal in response to drug activity with a compound to be screened for inhibiting activity; and
- (b) detecting the presence or absence of a signal or increase or decrease of a signal generated from the inhibiting activity, wherein the absence or decrease of the signal is indicative for a putative inhibitor.
22. The method of claim 20 or 21, wherein said cell is a cell of claim 8, obtained by the method of claim 10 or can be obtained by the transgenic non-human animal of claim 15 or 16.
23. A method of identifying and obtaining a pro-drug or drug capable of modulating the activity of a molecular variant of a MRP-1 polypeptide comprising the steps of:
- (a) contacting the host cell of claim 8, the cell obtained by the method of claim 10, the polypeptide of claim 11 or the solid support of claim 17 or 18 with the first molecule known to be bound by a MRP-1 polypeptide to form a first complex of said polypeptide and said first molecule;
- (b) contacting said first complex with a compound to be screened, and
- (c) measuring whether said compound displaces said first molecule from said first complex.
24. A method of identifying and obtaining an inhibitor capable of modulating the activity of a molecular variant of a MRP-1 polypeptide or its gene product comprising the steps of:
- (a) contacting the host cell of claim 8, the cell obtained by the method of claim 10, the protein of claim 11 or the solid support of claim 17 or 18 with the first molecule known to be bound by a MRP-1 polypeptide to form a first complex of said polypeptide and said first molecule;
- (b) contacting said first complex with a compound to be screened, and
- (c) measuring whether said compound displaces said first molecule from said first complex.

25. The method of claim 23 or 24, wherein said measuring step comprises measuring the formation of a second complex of said polypeptide and said compound.
26. The method of any one of claims 23 to 25, wherein said measuring step comprises measuring the amount of said first molecule that is not bound to said polypeptide.
27. The method of any one of claims 23 to 26, wherein said first molecule is labeled.
28. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 20 to 27; and the further step of formulating the compound identified and obtained or a derivative thereof in a pharmaceutically acceptable form.
29. A method of diagnosing a disorder related to the presence of a molecular variant of a MRP-1 gene or susceptibility to such a disorder comprising determining the presence of a polynucleotide of any one of claims 1 to 3 or the gene of claim 4 or 5 in a sample from a subject.
30. The method of claim 29 further comprising determining the presence of a polypeptide of claim 11 or the antibody of any one of claims 12 to 14.
31. A method of diagnosing a disorder related to the presence of a molecular variant of a MRP-1 gene or susceptibility to such a disorder comprising determining the presence of a polypeptide of claim 11 or the antibody of any one of claims 12 to 14 in a sample from a subject.
32. The method of any one of claims 29 to 31, wherein said disorder is a cancer disease or a disease related to multidrug resistance.

33. The method of any one of claims 29 to 32 comprising PCR, ligase chain reaction, restriction digestion, direct sequencing, nucleic acid amplification techniques, hybridization techniques or immunoassays.
34. A method of detection of the polynucleotide of any one of claims 1 to 3 or the gene of claim 4 or 5 in a sample comprising the steps of
 - (a) contacting the solid support of claim 17 or 18 with the sample under conditions allowing interaction of the polynucleotide of claim 1 to 3 or the gene of claim 4 or 5 with the immobilized targets on a solid support and;
 - (b) determining the binding of said polynucleotide or said gene to said immobilized targets on a solid support.
35. An in vitro method for diagnosing a disease comprising the steps of the method of claim 34, wherein binding of said polynucleotide or gene to said immobilized targets on said solid support is indicative for the presence or the absence of said disease or a prevalence for said disease.
36. A diagnostic composition comprising the polynucleotide of any one of claims 1 to 3, the gene of claim 4 to 5, the vector of claim 6 or 7, the polypeptide of claim 11 or the antibody of any one of the claims 12 to 14.
37. A pharmaceutical composition comprising the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5, the vector of claim 6 or 7, the polypeptide of claim 11 or the antibody of any of the claims 12 to 14.
38. Use of the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5, the vector of claim 6 or 7, the polypeptide of claim 11, the polynucleotides having at a position corresponding to position 926 of the MRP-1 gene (Accession No: U07050) a T insertion, at a position corresponding to position 79 of the MRP-1 gene (Accession No: AF022830) an A or at a position corresponding to position 137647 of the MRP-1 gene (Accession No: AC026452) a T, or at a position corresponding to position 150727 of the MRP-

1 gene (Accession No: AC025277) an A, or the antibody of any of the claims 12 to 14 for the preparation of a diagnostic composition for diagnosing a disease.

39. Use of the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5, the vector of claim 6 or 7, the polypeptide of claim 11, the polynucleotides having at a position corresponding to position 926 of the MRP-1 gene (Accession No: U07050) a T insertion, at a position corresponding to position 79 of the MRP-1 gene (Accession No: AF022830) an A or at a position corresponding to position 137647 of the MRP-1 gene (Accession No: AC026452) a T, or at a position corresponding to position 150727 of the MRP-1 gene (Accession No: AC025277) an A, or the antibody of any of the claims 12 to 14 for the preparation of a pharmaceutical composition for treating a disease.
40. The use of claim 38 or 39, wherein said disease is cancer or a disease related to multidrug resistance.
41. The use of claim 40 or the polynucleotide of claim 2, wherein said cancer disease is renal cancer.
42. A diagnostic kit for detection of a single nucleotide polymorphism comprising the polynucleotide of any one of claims 1 to 3, the gene of claim 4 or 5, the vector of claim 6 or 7, the polypeptide of claim 11, the antibody of any of the claims 12 to 14, the host cell of claim 8, the transgenic non-human animal of claim 15 or 16 or the solid support of claim 17 or 18.